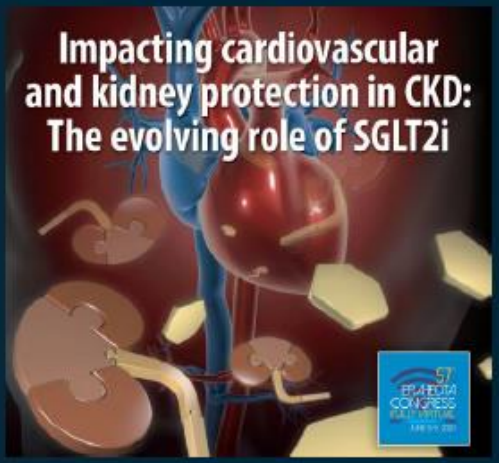

The cardiorenal connection & diabetes: Exploring opportunities for intervention

Dr. Maria Rosa Costanzo, MD
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The Cardiorenal Connection & Diabetes: Exploring Opportunities for Intervention

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Distinguishing Features of SGL2 Inhibitors

ause weight loss by exporting calories from the body to the urine

educe BP commensurate to their natriuretic effect

re uricosuric

- Inhibition of the tubular urate transporter URAT1
- Tubular fluid glucose trans-stimulate uric acid secretion by the facilitative glucose transporter GLUT9

o not cause hypoglycemia because glycosuric effect disappears hen blood glucose levels decline below 70mg/dL, as a result of ransport capacity residual in SGLT1 and because the drugs leave etabolic counter-regulation intact

eversibly lessen GFR (i.e. reduce hyperfiltration)by activating TGF

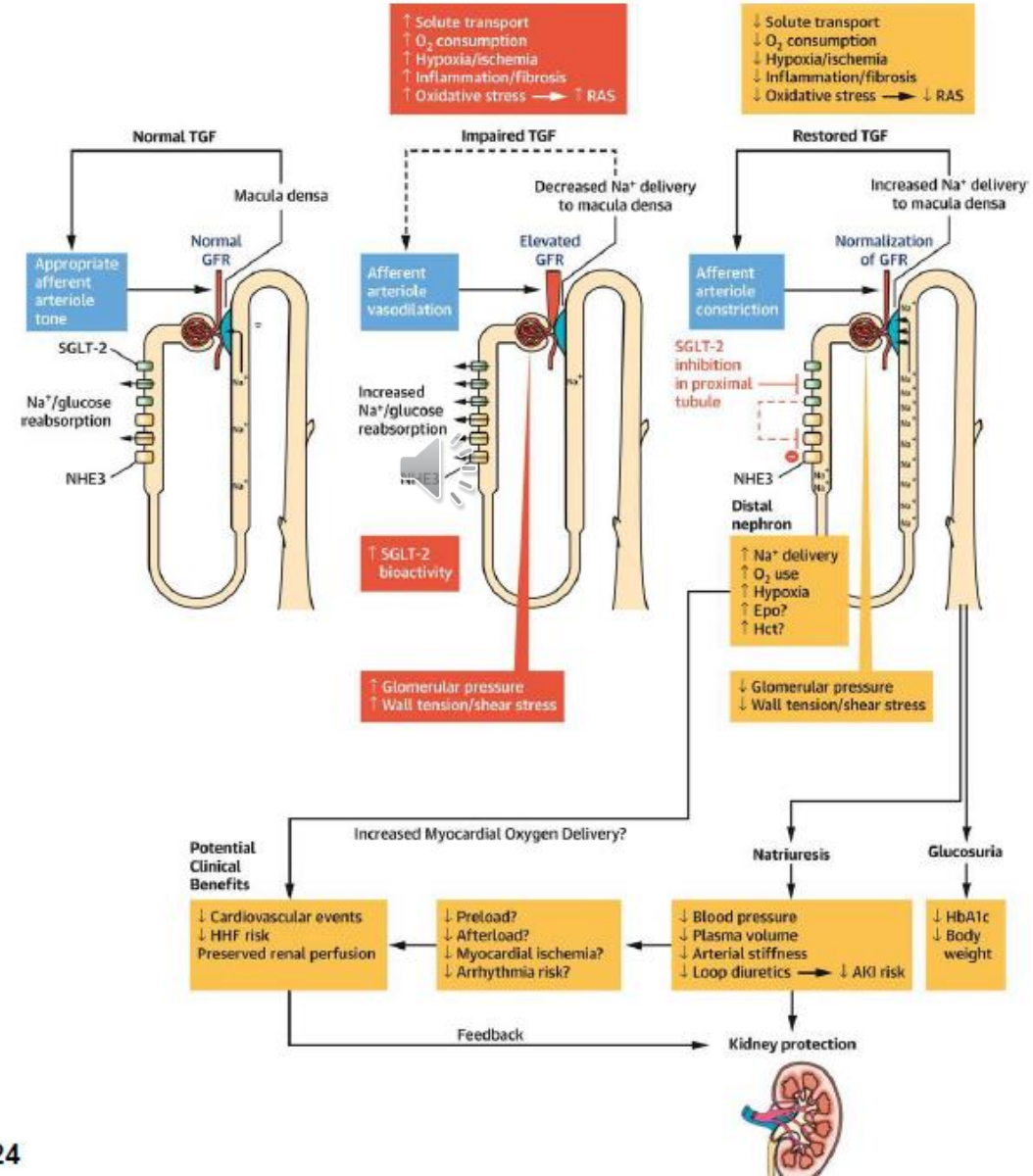
Anticipated Effects of SGLT2 Inhibitors on Clinical variables in T2DM Patients

Due to Decreased BV, Reduced Arterial Stiffness, Improved Endothelial Function

CKD Stage	SBP (53,54)	DBP (53,55)	HbA_{1c} (53,54,56)	Weight (53,54,56)	Albuminuria (57)	eGFR (54,56)	Uric Acid (58)	Hematocrit (59)
1-2	↓3-5 mm Hg	↓1-2 mm Hg	↓0.6-0.9%	↓2-3 kg	↓30%-50%	↓3-5 ml/min/1.73 m^2	↓10%-15%	↑3%-5%
3a	↓3-5 mm Hg	↓1-2 mm Hg	↓0.3-0.5%	↓1-2 kg	↓30%-50%	↓3-5 ml/min/1.73 m^2	↓10%-15%	↑3%-5%
3b	↓3-5 mm Hg	↓1-2 mm Hg	↔	↓1-2 kg	↓30%-50%	↓3-5 ml/min/1.73 m^2	↔	↑3%-5%
4	↓3-5 mm Hg	↓1-2 mm Hg	↔	↓1-2 kg	↓30%-50%	↓3-5 ml/min/1.73 m^2	NA	NA
5	NA	NA	NA	NA	NA	NA	NA	NA

David Z. Cherney et al. J Am Coll Cardiol 2019;74:2511-2524

Selected Physiological Mechanisms Associated With Cardiovascular and Renal Protection With SGLT2 Inhibitors



David Z. Cherney et al. J Am Coll Cardiol 2019;74:2511-2524

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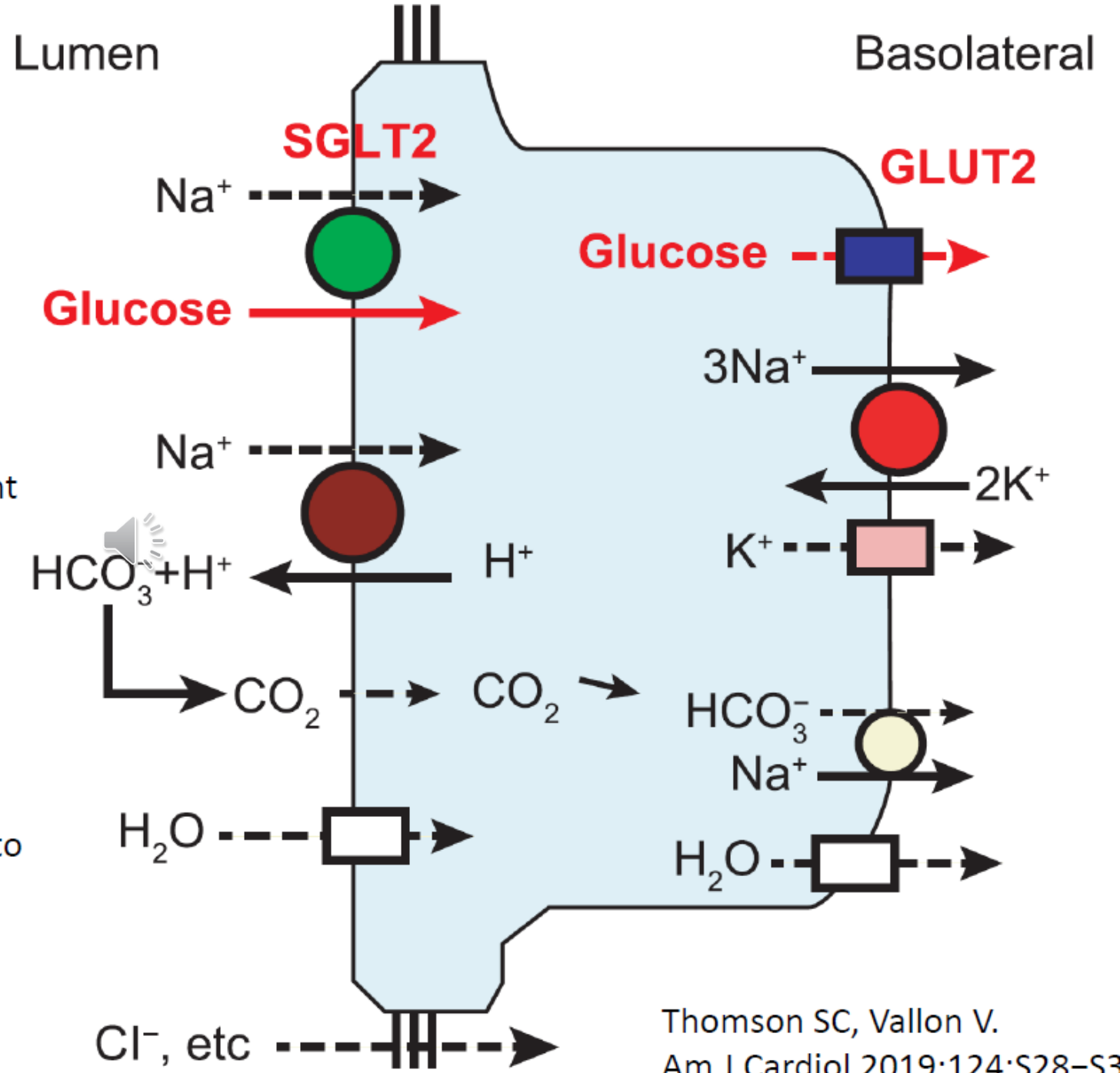
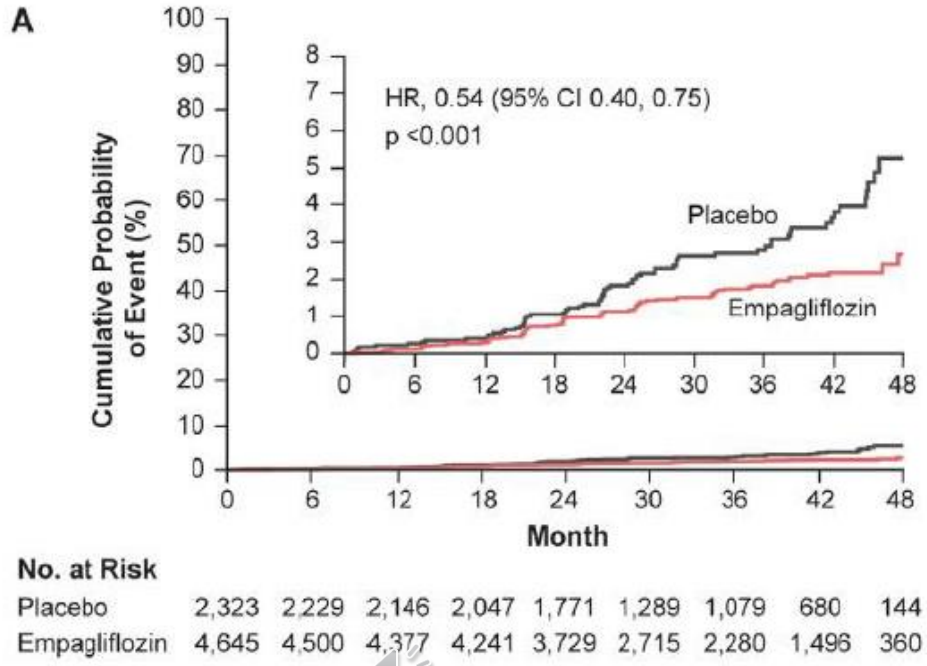
SGLT2 Mechanism in the Early Proximal Tubule

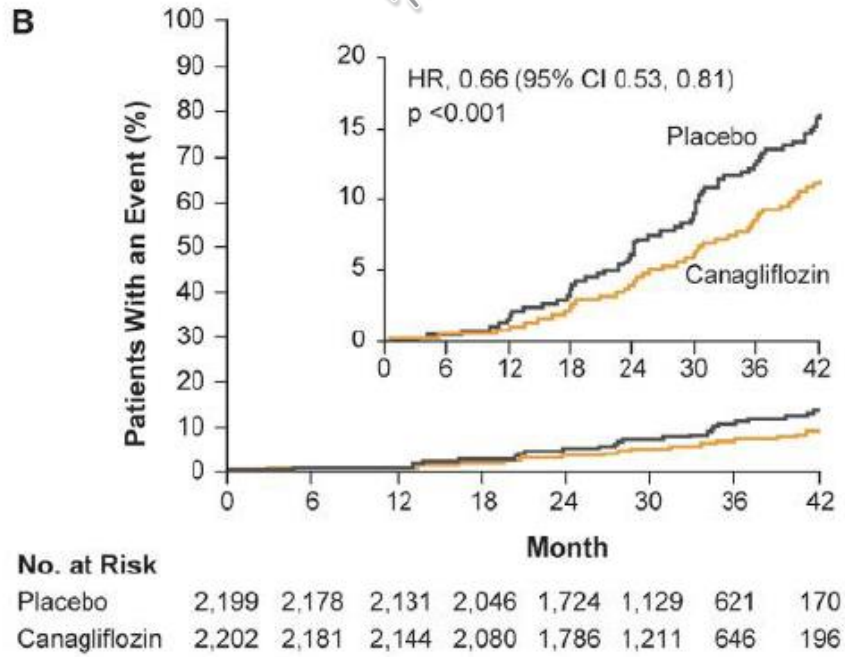
- ✓ Normal daily GF contains 1 mol (180 mg) glucose.
- ✓ If all excreted in the urine, loss of energy equivalent to 30% of body's caloric expenditure.
- ✓ SGLT1 and 2 can reabsorb 2.5 mol glucose/day.
- ✓ SGLT1 reabsorbs 2 Na per glucose; SGLT2 1 Na per glucose.
- ✓ SGLT2 reabsorbs 25% of Na linked to bicarbonate reabsorption.
- ✓ If filtered glucose rises to transport max. then the amount of Na that passes through SGLT increases to 19 mmol/L or 80% of Na directly linked to bicarbonate.
- ✓ Na reabsorption draws water, increasing Cl concentration and further increasing NaCl reabsorption.

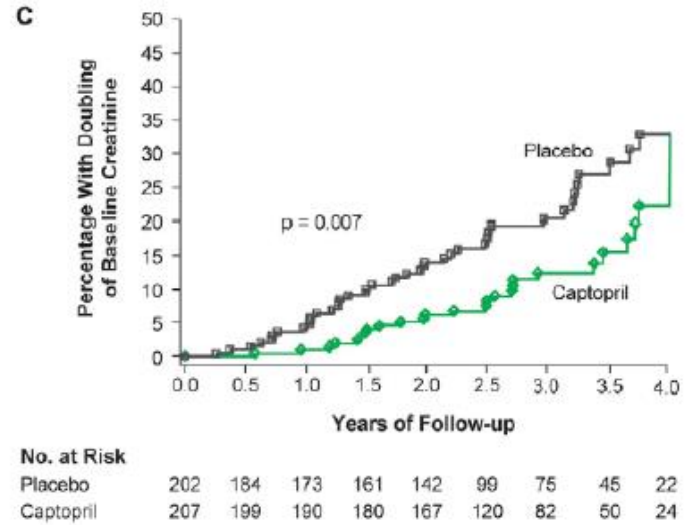


Thomson SC, Vallon V.
Am J Cardiol 2019;124:S28–S3

Renal Outcomes in SGLT2 Inhibitors and in Captopril Trials

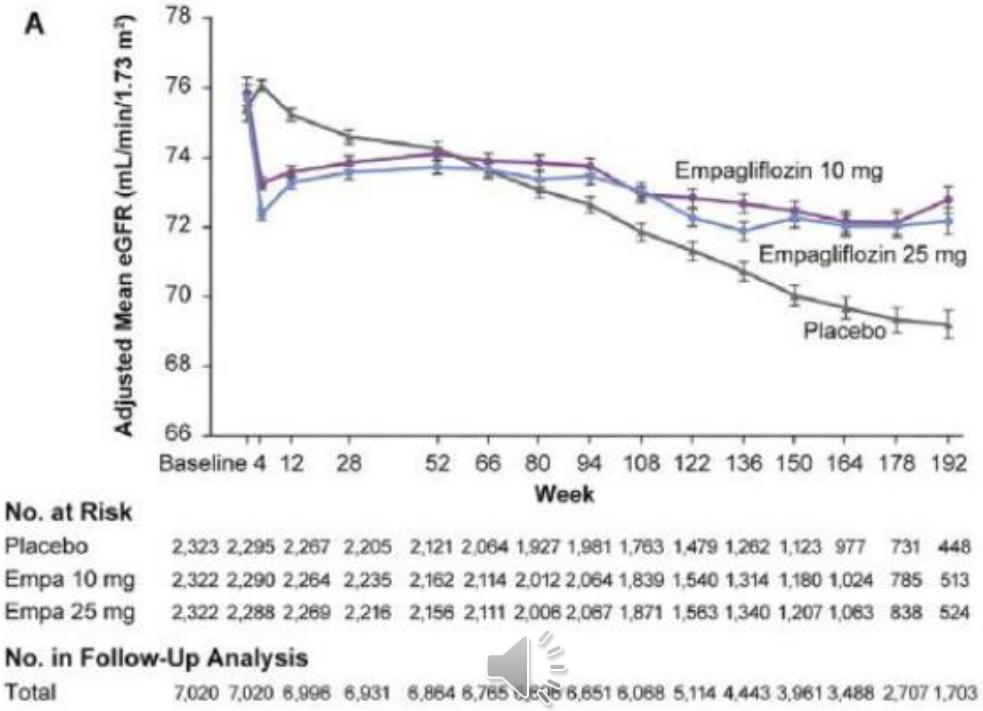


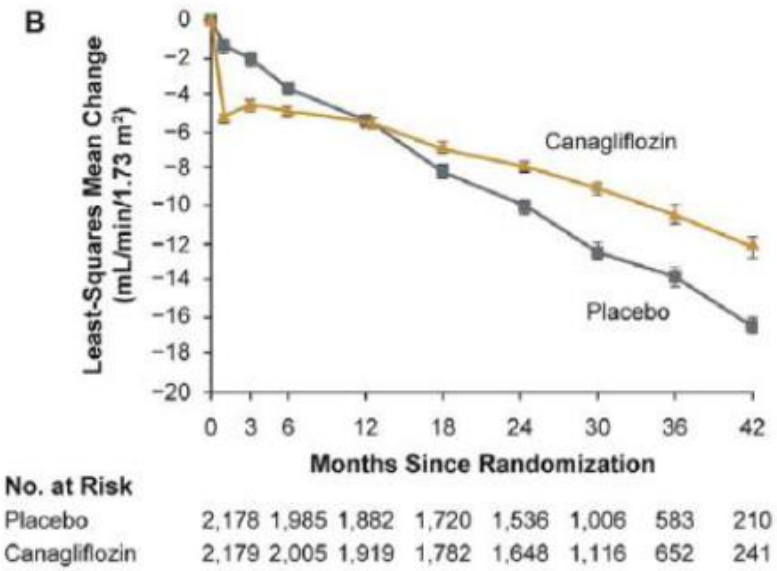


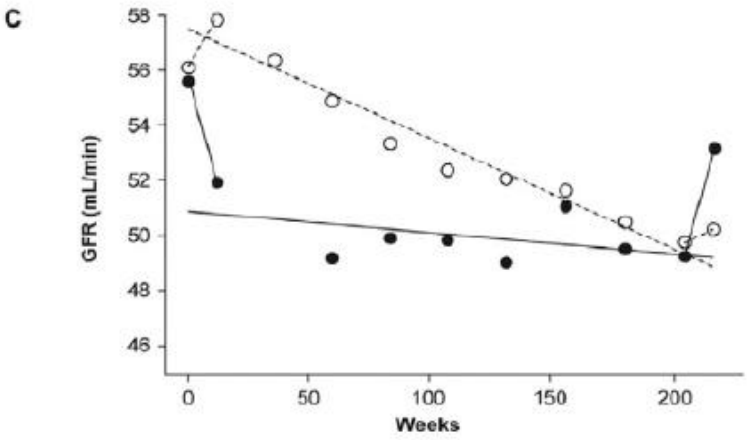


Thomson SC, Vallon V.
Am J Cardiol 2019;124:S28–S35

Similarity of eGFR Outcomes in SGLT2 Inhibitor Clinical Trials

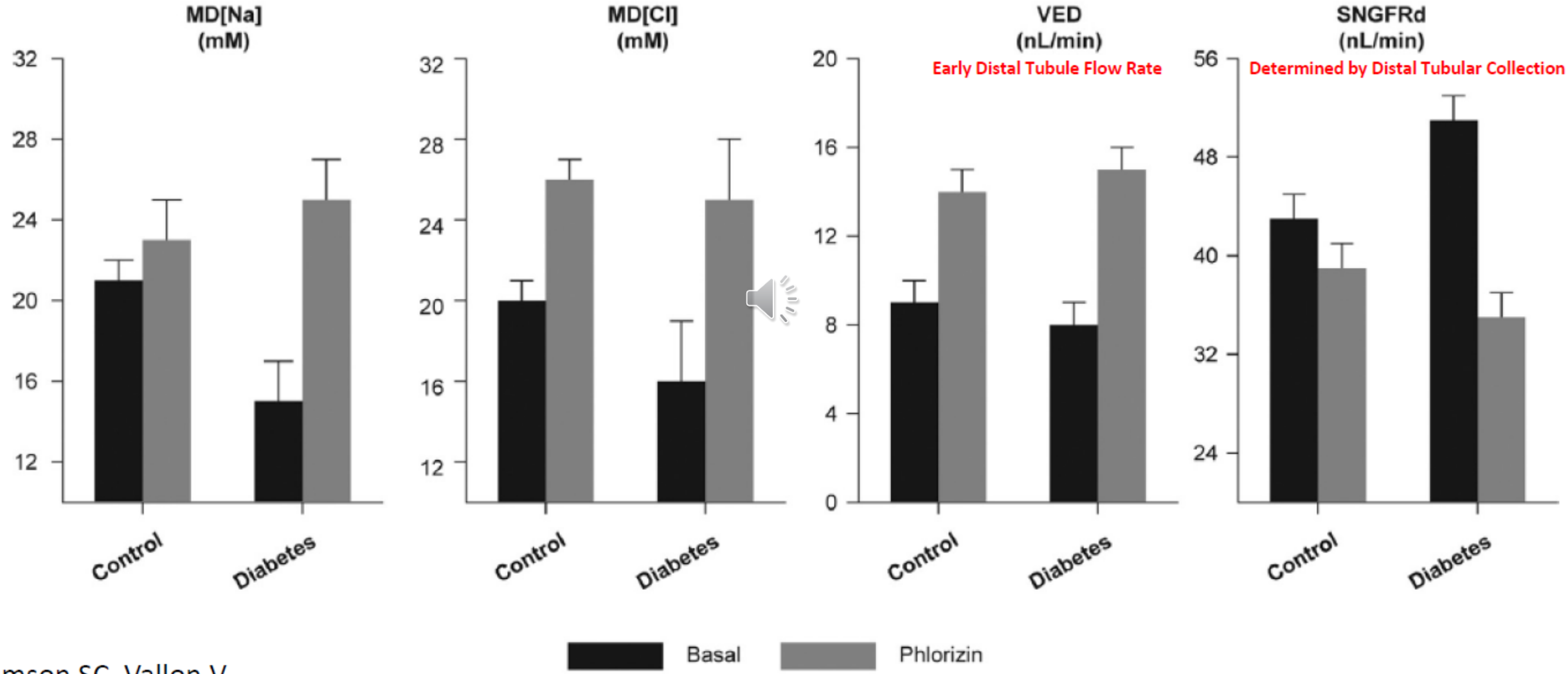






Thomson SC, Vallon V.
Am J Cardiol 2019;124:S28–S35

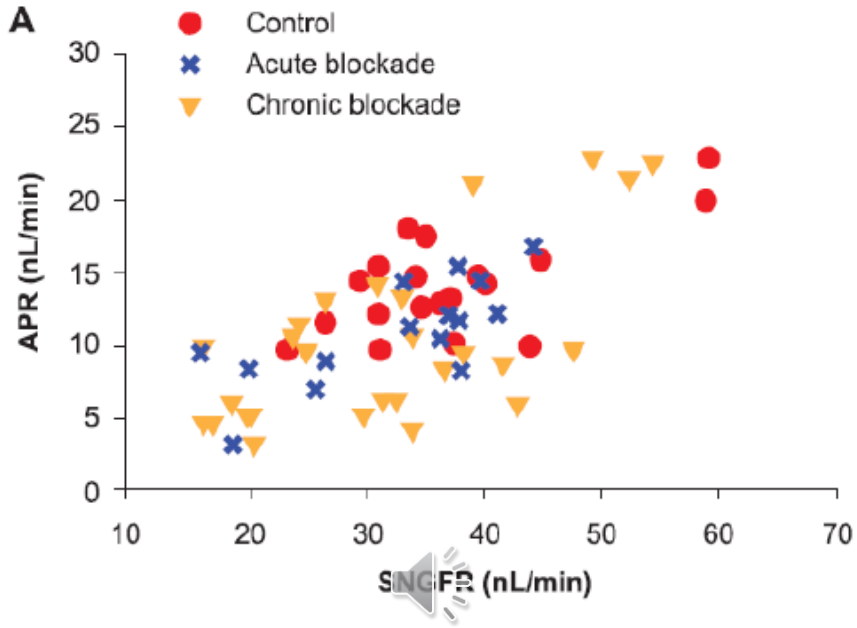
Immediate Effects of Phlorizin Delivered to Bowman's Space on Macula Densa Delivery of Na, Cl, Fluid Volume, and SNGFR Measured Downstream of the Macula Densa to Allow TGF to Operate.

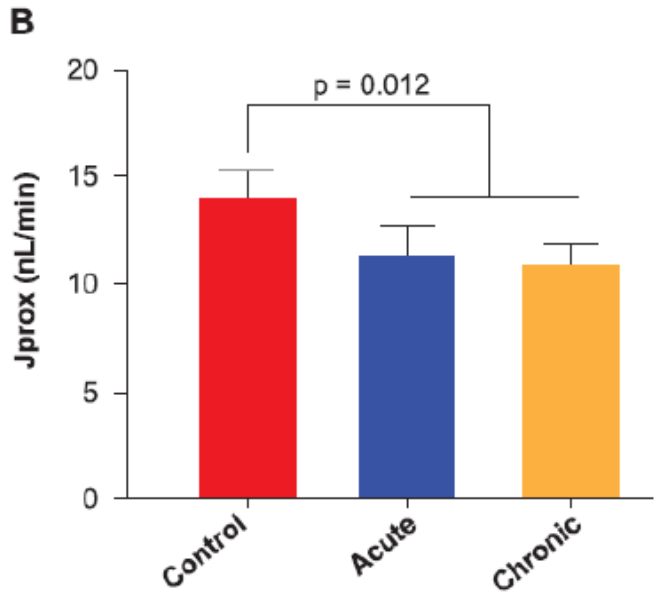


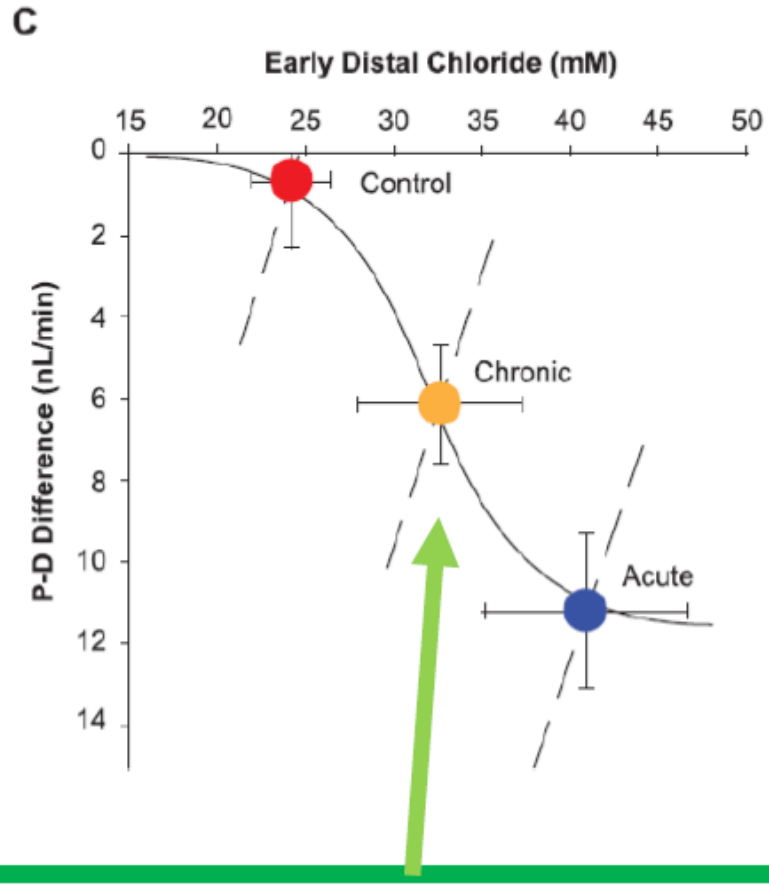
Thomson SC, Vallon V.
Am J Cardiol 2019;124:S28–S35

Acute and Chronic Effects of SGLT2 Blockade with Dapagliflozin on Tubular Reabsorption in a Rodent Model of Early Diabetes

Intact TGF



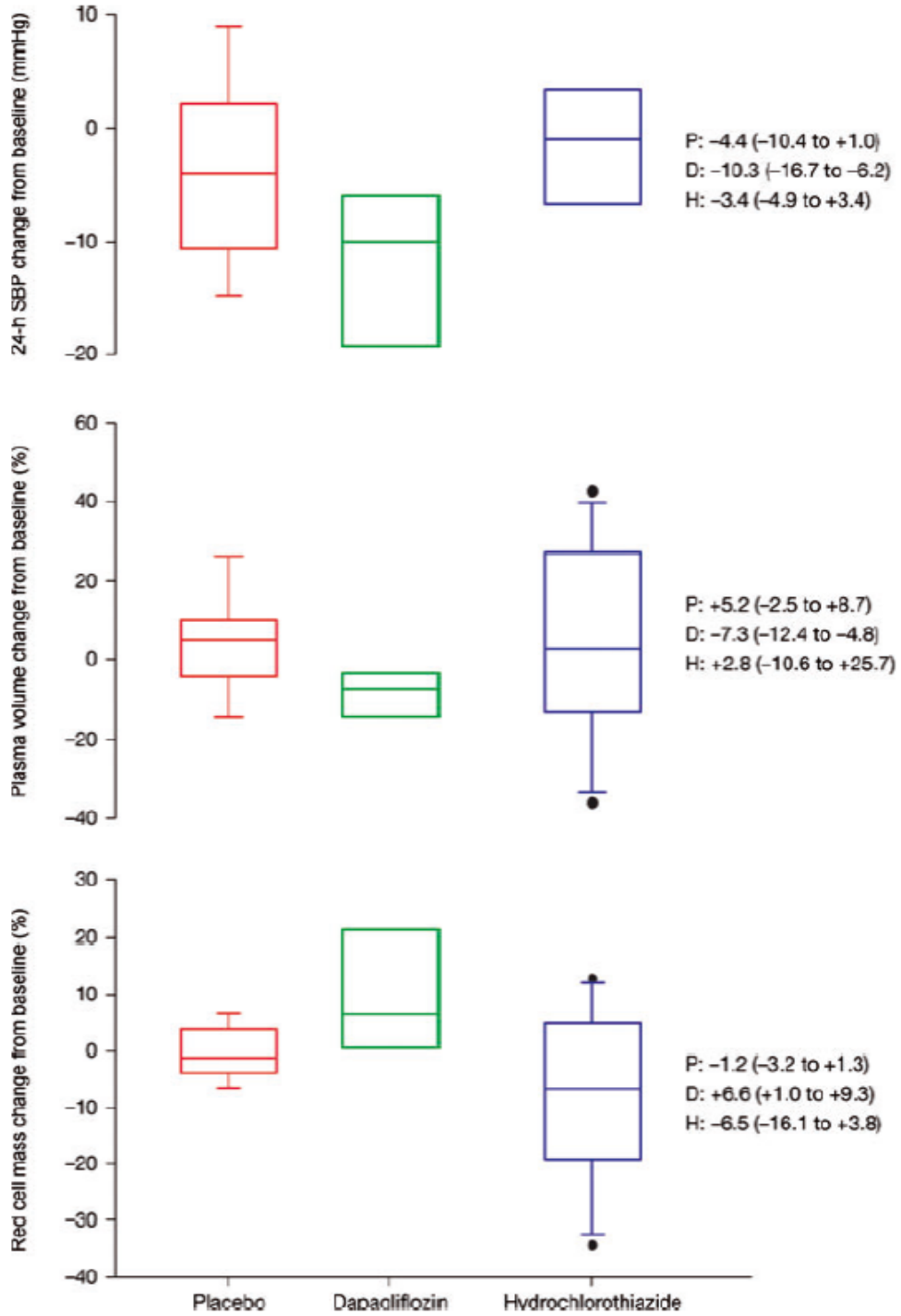




Attenuated Chronic Response due to Compensatory Reabsorption in the Loop of Henle

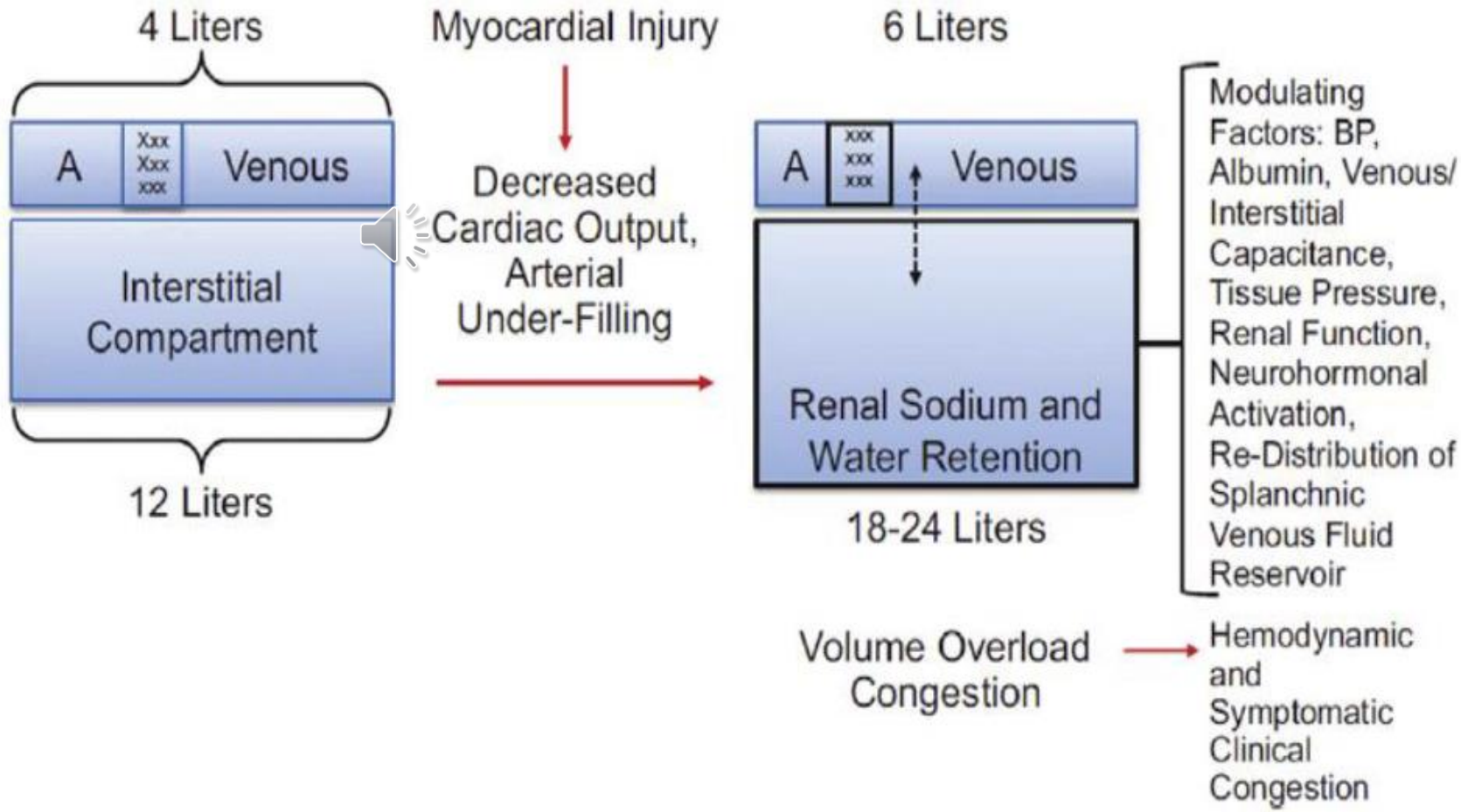
Thomson SC, Vallon V.
Am J Cardiol 2019;124:S28–S35

Median Change in 24-h Systolic BP and Median % Change in Plasma Volume and Red Cell Mass

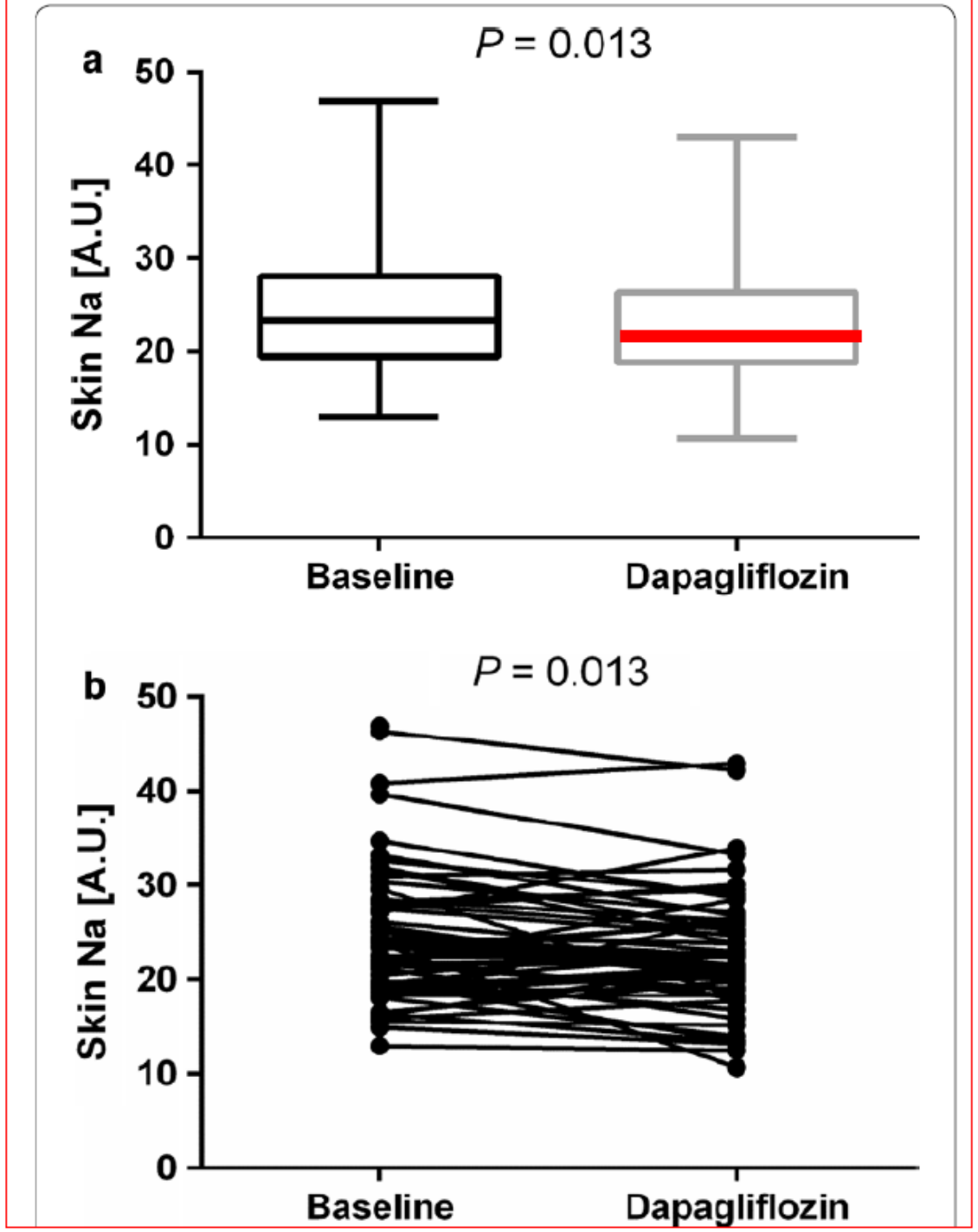


Lambers Heerspink HJ et al. Diabetes Obes Metab 2013;15: 853-63

Mechanisms of Interstitial and Intravascular Volume Expansion in HF



Miller WL. Circ Heart Fail. 2016;9: e002922.



Changes in Skin Sodium Content after 6 Week Treatment with SGLT2 Inhibitors

Karg MV et al. Cardiovasc Diabetol 2018; 17:

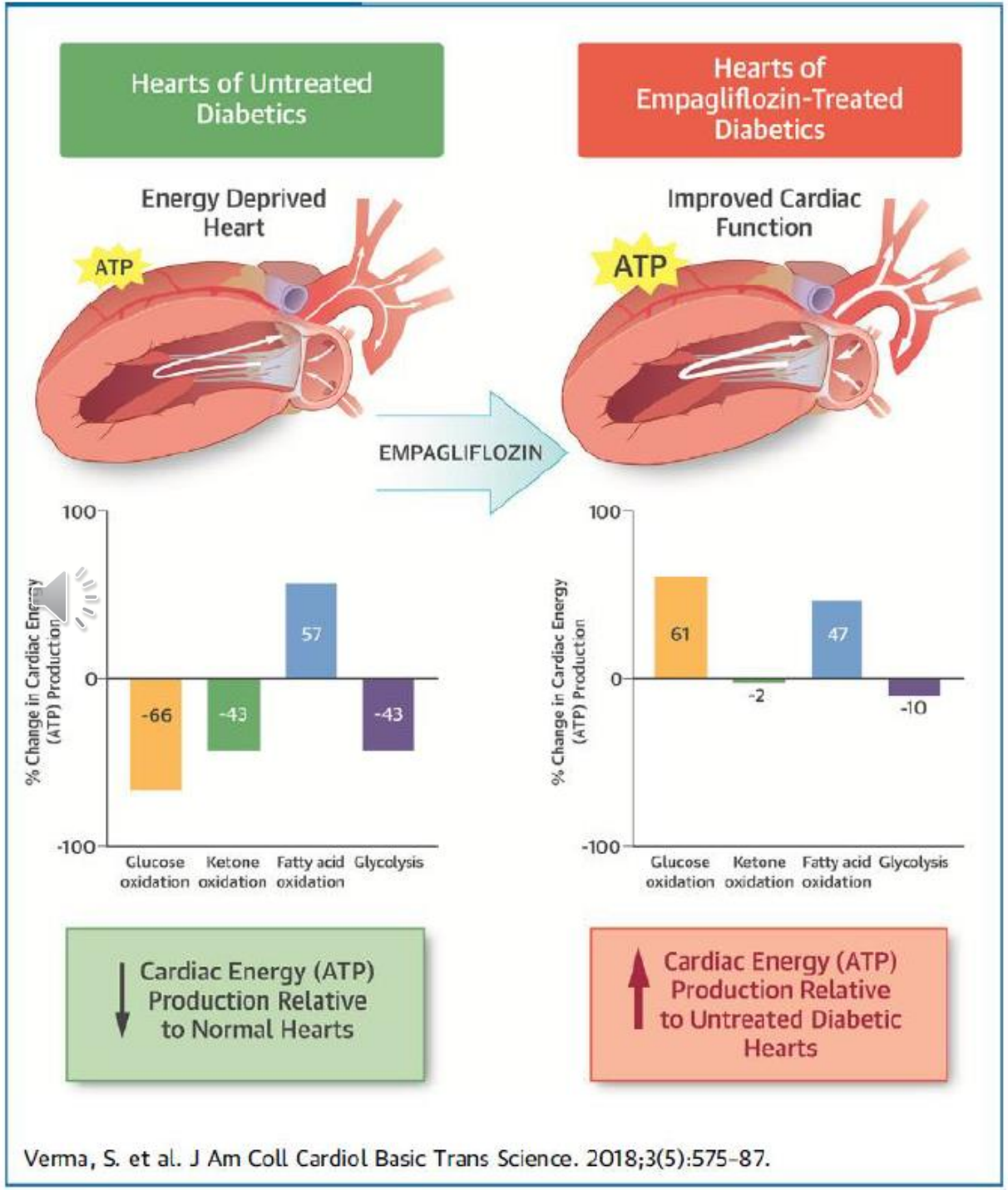
SGLT2 and Sodium-Hydrogen Exchange

- Co-localization and positive interference between SGLT2 and sodium-hydrogen exchanger (NHE)
- Inhibition of SGLT2 suppresses the activity of NHE3
- Knocking out tubular NHE3 reduces expression of SGLT2 and the natriuretic effect of SGLT2 blockade.
- The coupling may facilitate the GTB of sodium, glucose, and bicarbonate when GFR is increasing.
- Acid-base balance and glucose metabolism are already coupled through phosphoenolpyruvate carboxykinase
- (PEPCK), a key enzyme for both gluconeogenesis and the renal compensatory response for systemic acidosis.
- Blood glucose will rise whenever tubular PEPCK is stimulated by acidosis and systemic pH will rise when PEPCK is stimulated to perform gluconeogenesis.
- This confounding could be mitigated by having SGLT2 and NHE3 change in parallel because increasing SGLT2 to raise cell glucose above its equilibrium concentration would suppress
- PEPCK and increasing NHE3 expression would sustain ammonia secretion, thereby allowing the proximal tubule to perform its function as a regulator of systemic pH with less reliance on PEPCK
- empagliflozin suppresses NHE1 in cardiac myocytes, which do not express SGLT2

Metabolic and Macula Densa Effects

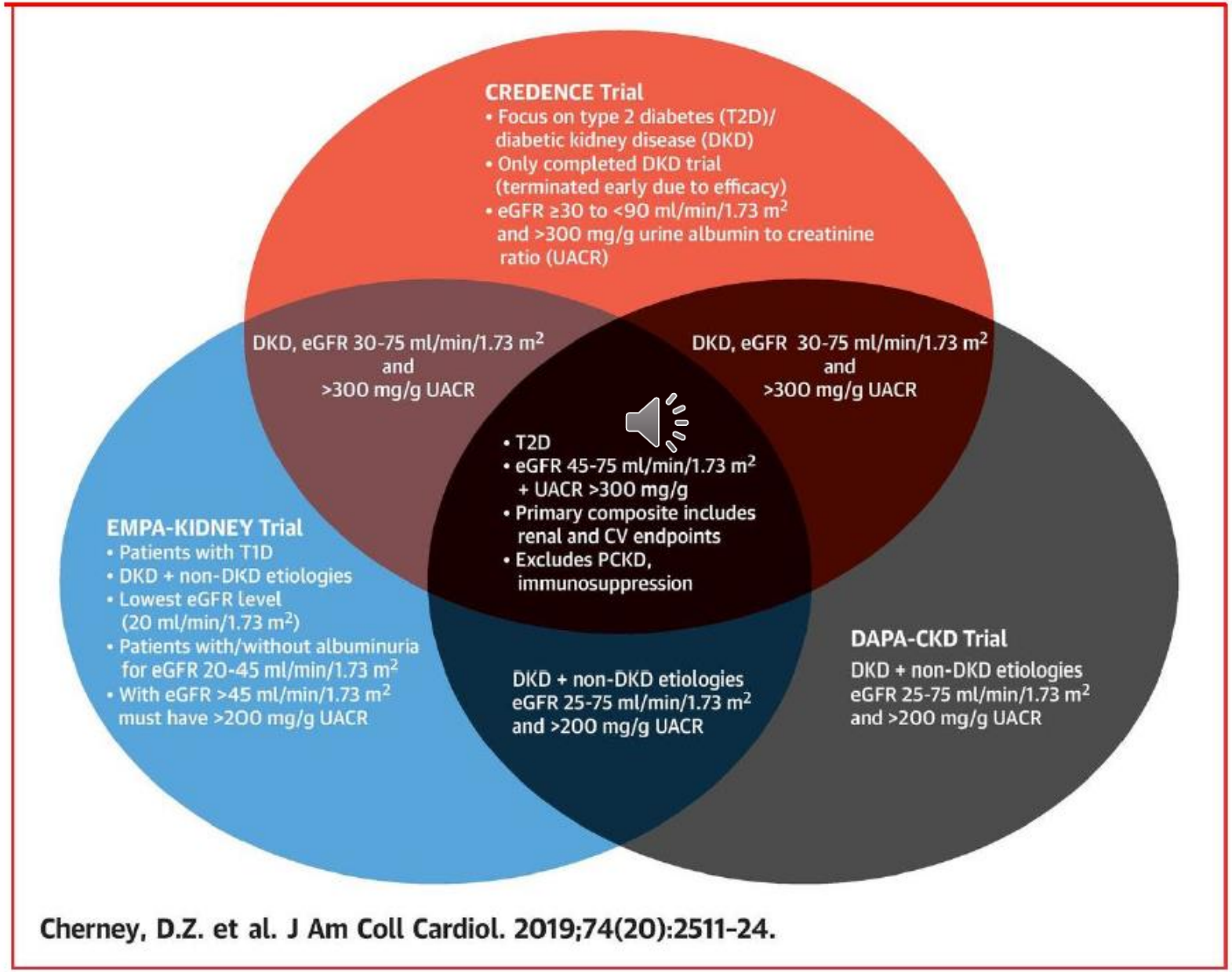
- SGLT2 inhibitors are ketogenic and thereby improve cardiac function (the heart requires less oxygen when generating ATP from ketones. SGLT2 could also benefit the diabetic kidney by this same mechanism, effectively reducing regional hypoxia.
- Blocking the macula densa nitric oxide synthase 1(NOS1) eliminates hyperfiltration in diabetic rats while having minimal impact on GFR in nondiabetic animals.
- Macula densa cells express SGLT1 and activating SGLT1 in MD triggers NOS1 activity.
- New studies show knockout of SGLT1 prevents diabetes-induced upregulation of NOS1 in the macula densa and mitigates glomerular hyperfiltration.
- Absence of SGLT1 also attenuates upregulation of macula densa NOS1 expression in response to SGLT2 inhibition in non-diabetic mice.
- Effects of SGLT1 and SGLT2 inhibition on diabetic glomerular hyperfiltration are additive.

Empagliflozin Increases Cardiac Energy Production in Diabetes



Verma, S. et al. J Am Coll Cardiol Basic Trans Science. 2018;3(5):575–87.

Areas of Overlap for Clinical Trials with SGLT2 in Patients with CKD



Cherney, D.Z. et al. J Am Coll Cardiol. 2019;74(20):2511-24.

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All-Cause Mortality, CV Events, and Renal Outcomes in CVOTs of SGLT-2 Inhibitors

- Reduction in albuminuria and hard renal outcomes:
  - Over a wide range of baseline HgbA1c
  - Across albuminuria ranges
  - With and without baseline renal impairment
- In DECLARE renal benefit occurred even though renal risk was low at baseline (eGFR 85 ml/min/1.73m^2)

A

Outcome	Total Events	Participants	Empagliflozin	Placebo	EMPA-REG OUTCOME	HR [95%-CI]	IRR in 1,000 pts. Over 3 yrs [95%-CI]	NNT Over 3 yrs [95%-CI]
			events per 1,000 patient years					
Primary Outcome								
MACE	772	7,020	37.4	43.9		0.86 [0.74-0.99]	-19.5 [-37.8 to -1.2]	52 [27 to 834]
All-Cause Mortality								
All-Cause Mortality	463	7,020	19.4	28.6		0.68 [0.57-0.82]	-27.6 [-41.5 to -13.7]	37 [25 to 73]
Cardiovascular Outcomes								
Cardiovascular Mortality	309	7,020	12.4	20.2		0.62 [0.49-0.77]	-23.4 [-35.0 to -11.8]	43 [29 to 85]
Hospitalization for Heart Failure	221	7,020	9.4	14.5		0.65 [0.50-0.85]	-15.3 [-25.3 to -5.3]	66 [40 to 189]
Myocardial Infarction	349	7,020	16.8	19.3		0.87 [0.70-1.09]	-7.5 [-19.6 to 4.6]	134 [52 to ∞]
Stroke	233	7,020	12.3	10.5		1.18 [0.89-1.56]	5.4 [-3.9 to 14.7]	186 [257 to ∞]
Renal Outcomes								
Renal Composite	152	6,968	6.3	11.5		0.54 [0.40-0.75]	-15.6 [-24.6 to -6.6]	65 [41 to 152]
ESKD	27	7,020	1	2.1		0.45 [0.21-0.97]	-3.3 [-7.0 to 0.4]	304 [143 to 2,500]
dSCr	130	6,968	5.5	9.7		0.56 [0.39-0.79]	-12.6 [-20.9 to -4.3]	80 [48 to 233]

0.5 1 2
Favors SGLT2 Favors Placebo

B

Outcome	Total Events	Participants	Canagliflozin	Placebo	CANVAS PROGRAM	HR [95%-CI]	IRR in 1,000 pts. Over 3 yrs [95%-CI]	NNT Over 3 yrs [95%-CI]
			events per 1,000 patient years					
Primary Outcome								
MACE	1,011	10,142	26.9	31.5		0.86 [0.75-0.97]	-13.8 [-24.7 to -2.9]	73 [41 to 345]
All-Cause Mortality								
All-Cause Mortality	681	10,142	17.3	19.5		0.87 [0.74-1.01]	-6.6 [-15.0 to 1.8]	152 [67 to ∞]
Cardiovascular Outcomes								
Cardiovascular Mortality	433	10,142	11.6	12.8		0.87 [0.72-1.06]	-3.6 [-10.4 to 3.2]	278 [97 to ∞]
Hospitalization for Heart Failure	353	10,142	5.5	8.7		0.67 [0.52-0.87]	-9.6 [-15.0 to -4.2]	105 [67 to 239]
Myocardial Infarction	421	10,142	11.2	12.6		0.89 [0.73-1.09]	-5.7 [-11.9 to 0.5]	176 [85 to ∞]
Stroke	309	10,142	7.9	9.6		0.87 [0.69-1.09]	-5.1 [-11.0 to 0.8]	197 [91 to ∞]
Renal Outcomes								
Renal Composite	73	10,140	1.5	2.8		0.53 [0.33-0.84]	-3.9 [-6.9 to -0.9]	257 [145 to 1,112]
ESKD	18	10,140	0.4	0.6		0.77 [0.30-1.97]	-0.6 [-2.0 to 0.8]	1,667 [500 to ∞]
dSCr	60	10,140	1.2	2.4		0.50 [0.30-0.84]	-3.6 [-6.4 to -0.8]	278 [157 to 1,250]

0.5 1 2
Favors SGLT2 Favors Placebo

C

Outcome	Total Events	Participants	Dapagliflozin	Placebo	DECLARE-TIMI 58	HR [95%-CI]	IRR in 1,000 pts. Over 3 yrs [95%-CI]	NNT Over 3 yrs [95%-CI]
			events per 1,000 patient years					
Co-Primary Outcomes								
Cardiovascular Mortality or Hospitalization for Heart Failure	913	17,160	12.2	14.7		0.83 [0.73-0.95]	-7.5 [-12.7 to -2.3]	134 [79 to 435]
MACE	1,559	17,160	22.6	24.2		0.93 [0.84-1.03]	-4.8 [-11.8 to 2.2]	209 [85 to ∞]
All-Cause Mortality								
All-Cause Mortality	1,099	17,160	15.1	16.4		0.93 [0.82-1.04]	-3.9 [-9.5 to 1.7]	257 [106 to ∞]
Cardiovascular Outcomes								
Cardiovascular Mortality	494	17,160	7	7.1		0.98 [0.82-1.17]	-0.3 [-4.0 to 3.4]	3,334 [250 to ∞]
Hospitalization for Heart Failure	498	17,160	6.2	8.5		0.73 [0.61-0.88]	-6.9 [-10.8 to -3.0]	145 [93 to 334]
Myocardial Infarction	834	17,160	11.7	13.2		0.89 [0.77-1.01]	-4.5 [-9.6 to 0.6]	223 [105 to ∞]
Stroke	466	17,160	6.9	6.8		1.01 [0.84-1.21]	0.3 [-3.4 to 4]	3,334 [295 to ∞]
Renal Outcomes								
Renal Composite	365	17,160	3.7	7		0.53 [0.43-0.66]	-9.9 [-13.2 to -6.6]	102 [76 to 152]

0.5 1 2

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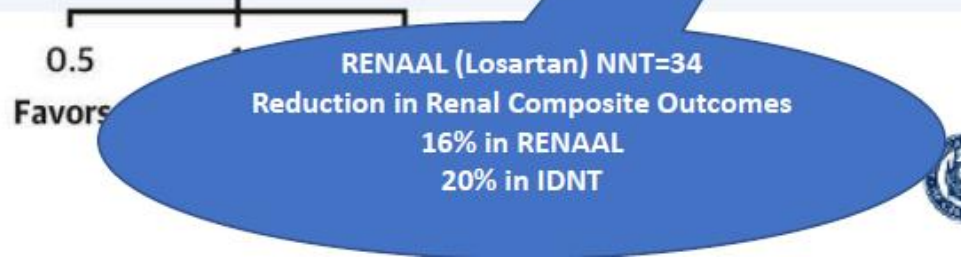
All-Cause Mortality, CV Events, and Renal Outcomes in the CREDENCE Trial

Outcome	Total Events	Participants	Canagliflozin	Placebo	CREDENCE	HR [95%-CI]	IRR in 1,000 pts. Over 3 yrs [95%-CI]	NNT Over 3 yrs [95%-CI]
			events per 1,000 patient years					
Primary Outcome								
dSCr, ESKD, Renal or CV Death	585	4,401	43.2	61.2		0.70 [0.59-0.82]	-54.0 [-79.4 to -28.6]	19 [13 to 35]
All-Cause Mortality								
All-Cause Mortality	369	4,401	29.0	35.0		0.83 [0.68-1.02]	-18.0 [-37.6 to 1.6]	56 [27 to ∞]
Renal Outcomes								
Renal Composite	377	4,401	27.0	40.4		0.66 [0.53-0.81]	-40.2 [-60.6 to .8]	25 [17 to 51]
ESKD	281	4,401	20.4	29.4		0.68 [0.54-0.86]	-27.0 [-44 -9.5]	38 [23 to 106]
dSCr	306	4,401	20.7	33.8		0.60 [0.48-0.76]	-39.3 [- -21.0]	26 [18 to 48]
Cardiovascular Outcomes								
Cardiovascular Mortality	250	4,401	19.0	24.4		0.78 [0.61-1.00]	-32.3 to -0.0]	62 [31 to ∞]
MACE	486	4,401	38.7	48.7		0.80 [0.67-0.95]	[-53.3 to -6.7]	34 [19 to 150]
Hospitalization for Heart Failure	230	4,401	15.7	25.3		0.61 [0.47-0	.8 [-44.7 to -12.9]	35 [23 to 78]



David Z. Cherney et al. J Am Coll Cardiol 2019;74:2511-2524

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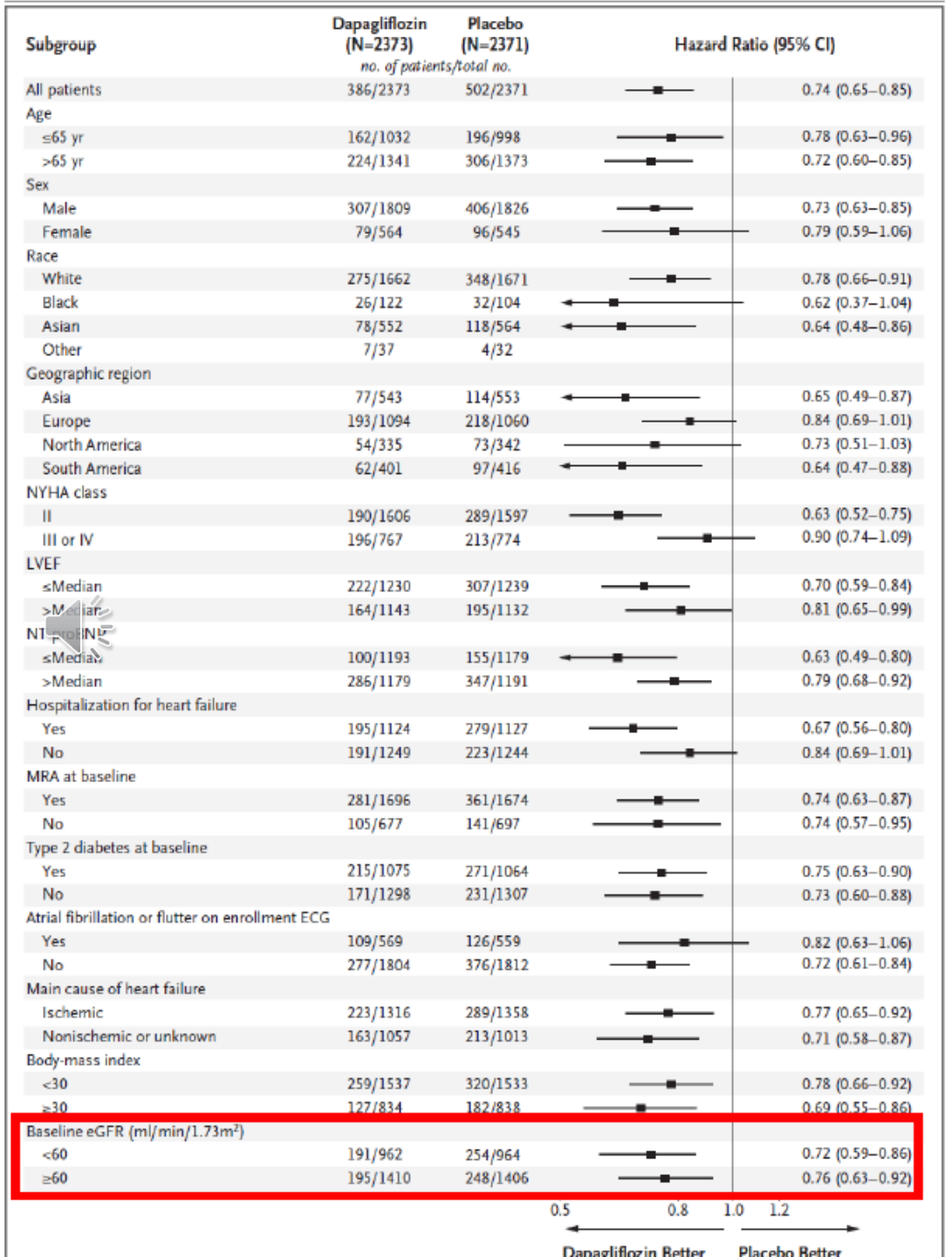
DAPA-HF Primary Endpoint According to Pre-Specified Subgroups



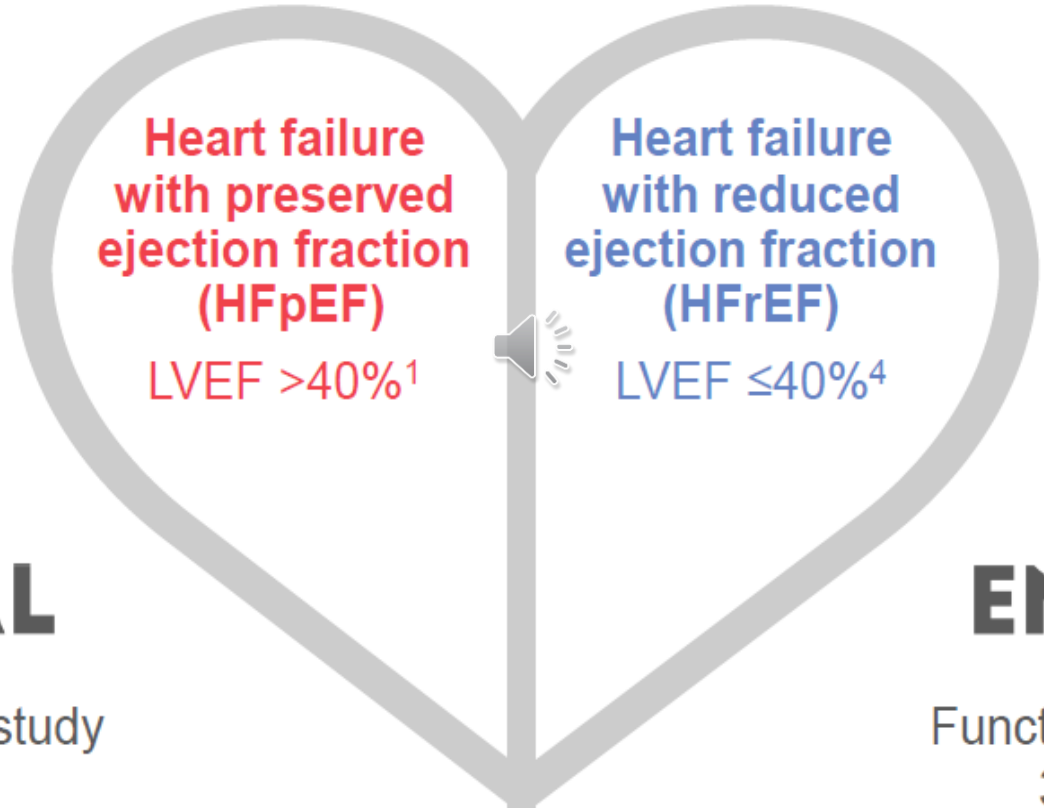
Subgroup	Dapagliflozin (N=2373) no. of patients/total no.	Placebo (N=2371) no. of patients/total no.	Hazard Ratio (95% CI)
All patients	386/2373	502/2371	0.74 (0.65–0.85)
Age			
≤65 yr	162/1032	196/998	0.78 (0.63–0.96)
>65 yr	224/1341	306/1373	0.72 (0.60–0.85)
Sex			
Male	307/1809	406/1826	0.73 (0.63–0.85)
Female	79/564	96/545	0.79 (0.59–1.06)
Race			
White	275/1662	348/1671	0.78 (0.66–0.91)
Black	26/122	32/104	0.62 (0.37–1.04)
Asian	78/552	118/564	0.64 (0.48–0.86)
Other	7/37	4/32	
Geographic region			
Asia	77/543	114/553	0.65 (0.49–0.87)
Europe	193/1094	218/1060	0.84 (0.69–1.01)
North America	54/335	73/342	0.73 (0.51–1.03)
South America	62/401	97/416	0.64 (0.47–0.88)
NYHA class			
II	190/1606	289/1597	0.63 (0.52–0.75)
III or IV	196/767	213/774	0.90 (0.74–1.09)
LVEF			
≤Median	222/1230	307/1239	0.70 (0.59–0.84)
>Median	164/1143	195/1132	0.81 (0.65–0.99)
NT-proBNP			
≤Median	100/1193	155/1179	0.63 (0.49–0.80)
>Median	286/1179	347/1191	0.79 (0.68–0.92)
Hospitalization for heart failure			
Yes	195/1124	279/1127	0.67 (0.56–0.80)
No	191/1249	223/1244	0.84 (0.69–1.01)
MRA at baseline			
Yes	281/1696	361/1674	0.74 (0.63–0.87)
No	105/677	141/697	0.74 (0.57–0.95)
Type 2 diabetes at baseline			
Yes	215/1075	271/1064	0.75 (0.63–0.90)
No	171/1298	231/1307	0.73 (0.60–0.88)
Atrial fibrillation or flutter on enrollment ECG			
Yes	109/569	126/559	0.82 (0.63–1.06)
No	277/1804	376/1812	0.72 (0.61–0.84)
Main cause of heart failure			
Ischemic	223/1316	289/1358	0.77 (0.65–0.92)
Nonischemic or unknown	163/1057	213/1013	0.71 (0.58–0.87)
Body-mass index			
<30	259/1537	320/1533	0.78 (0.66–0.92)
≥30	127/834	182/838	0.69 (0.55–0.86)
Baseline eGFR (ml/min/1.73m²)			
<60	191/962	254/964	0.72 (0.59–0.86)
≥60	195/1410	248/1406	0.76 (0.63–0.92)

Mc Murray JJV et al.
N Engl J Med 2019;381:1995-2008.

Conclusions

- Patients with T2DM have high residual risk for the development of cardiovascular complications and diabetic kidney disease progression.
- SGLT2 inhibitors have consistently reduced the risk of hospitalization for HF and progression of diabetic kidney disease.
- Selection of antihyperglycemic agents in patients with T2DM should take several factors into account, including metabolic requirements, safety, and background presence of CVD, HF, and renal complications.
- Ongoing and future trials are required to determine the safety and efficacy of SGLT2 inhibitors in novel settings, including in nondiabetic adults with CVD and/or kidney disease, and in individuals with CVD in the absence of T2DM.

The empagliflozin chronic heart failure program



EMPEROR
PRESERVED

Outcomes trial with planned recruitment:
5500 patients[1,2]

EMPEROR
REDUCED

Outcomes trial with planned recruitment:
3350 patients[3,4]

EMPERIAL
PRESERVED

Functional capacity study
300 patients[5,6]

EMPERIAL
REDUCED

Functional capacity study
300 patients[7,8]

EMPA-VISION

Mechanistic study
86 patients[9]